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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,604	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/22/05 has been entered.

1. Formal Matters

A. Claims 119-126 and 129-1313 are pending and are the subject of this Office Action.

B. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

C. The Declaration under 37 CFR 1.132 has been entered into the record.

2. Priority

A. As discussed in the below rejection under 35 USC 101, the priority date remains 11/14/01, the filing date of the instant invention.

3. Specification

A. Pages 303-306 of the specification are missing. Applicants are required to submit these pages. **Since Applicants' amendments ("native sequences") are supposedly supported on page 304 a new matter rejection will be made if Applicants do not supply the missing pages.**

4. Declaration under 37 CFR 1.132

A. The Declaration by Audrey Goddard under 37 CFR 1.132 has been considered, but is not deemed persuasive for the reasons discussed below in the rejection under 35 USC 101.

5. Claim Rejections - 35 USC § 101

A. Claims 119-126 and 129-131 remain rejected under 35 USC 101 for the reasons already of record on pages 3-6 of the Office Action mailed 7/26/04. Applicants recite numerous case law and argue that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently

available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining 'substantial' utility." (MPEP 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101."

Applicants further argue that "the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Absolute predictability is not a requirement." Applicants argue "that it is not a legal requirement to establish a 'necessary' correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted." They continue by arguing that there does not need to be a strong correlation between increase copy number (mRNA) and protein expression as long as the artisan believes there is a positive correlation. These arguments have been considered, but are not deemed persuasive. First, the Examiner is not necessarily questioning the relationship between mRNA copy number and protein levels. The issue is the lack of correlation between DNA levels and protein levels.

Applicants argue that the DNA of the present invention was significantly amplified in two out of two tumors and that, based on this, it would be expected that the polypeptide would also be amplified. This argument has been considered, but is not deemed persuasive. Even though in some circumstances and as discussed in the Goddard Declaration, TaqMan™ real-time PCR can accurately and reproducibly assess gene amplification, in cancerous tissues it is necessary to account for the possibility of aneuploidy. This rebuttal of Applicants' arguments is supported on page 4, lines 17-21 of Sen et al. (Curr. Opin. Oncol., 2000). Sen teaches that "numeric aberrations in chromosomes, referred to as aneuploidy, is commonly observed in human cancer." Therefore, because the gene amplification observed for PRO1281 is small and could reasonably be expected to be due to aneuploidy, the implicit utility of a colon tumor diagnostic is not specific and substantial.

Applicants argue that Pennica do not teach any correlation to increased genes in general, only specifically for the WISP family. What can be gathered from Pennica, in the view of the Examiner, is that, based on the fact that one gene increased in cancer and one did not, that there is only a 50% chance of a gene increasing in a particular cancer. To further add to the unpredictability of gene overexpression in tumors, Applicants argue that Pennica teaches that this overexpression was seen in only 84% of tumors examined. Therefore, given the fact that there is only a 50% chance of finding a gene which may be

overexpressed in tumors and that this gene is not even overexpressed on every occasion (84%), it seems difficult to predict that a gene will be overexpressed. In fact, in considering the information of Pennica, it seems more likely than not that a gene will *not* be overexpressed.

Applicants further argue that the Examiner's citing of Konopka was inappropriate since Konopka only teach the *abl* gene. This argument has been considered, but is not deemed persuasive. In fact, Konopka supports the Examiner's position that protein levels cannot be predicted from gene expression. This can be seen in Applicants' quotation from Konopka which states "Konopka et al. actually state that protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl m'RNA produced from a single Ph template." This, in view of Pennica, make a strong argument about predicting protein levels from DNA overexpression.

Though Haynes do not compare gene expression and protein levels, they do teach transcript levels and state that "correlation is 'not linear' and hence, 'one cannot accurately predict protein levels from mRNA [transcript] levels." Even if, as argued by Applicants, Haynes shows that it is more likely than not that mRNA levels correlate to protein levels, the present invention does not disclose mRNA levels, only DNA levels. Given the fact that Haynes is silent to DNA levels it can be assumed, especially in light of Pennica and Konopka, that DNA levels are not correlated (in general) to protein expression levels. Applicants argue that Omtoft, Pollack and Hyman show a general trend between protein and mRNA levels. Again, however, the present specification is concerned with DNA levels, not mRNA.

Applicants further argue the Ashkenazi Declaration and state that even the absence of a correlation or increased protein expression can still provide valuable information for cancer diagnosis and treatment. Applicants are also using a teaching by Hanna and Morin to support this assumption. Applicants, therefore, conclude "that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor." However, Hanna go on to state that "'FISH (gene) and IHC (protein) results correlate well. However, subsets of tumors are found which show discordant results; i.e. protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear.' Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor."

6. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-126 and 129-131 remain rejected under 35 USC 112 for the reasons already of record on page 6 of the Office Action mailed 7/26/04 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

B. Claims 119-123 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 6-7 of the Office Action mailed 7/26/04. Applicants argue that the "signal sequence" was disclosed in the specification as residues 1-15 (Example 102 on page 435). However, line 35 of that page discloses that the signal sequence is "about residues 1-15." Therefore, at the time of filing of the present invention, even Applicants, themselves, were unsure of the actual signal sequence. Therefore, contrary to Applicants' assertion, the ordinarily skilled artisan would not know the actual sequence of the signal peptide and, therefore, the "mature" sequence (i.e. without the signal sequence).

Applicants argue that the claimed invention fulfills the Wands factors and, with or without the signal sequence, the artisan would know how to use the polypeptide of the invention in the diagnosis and characterization of colon tumors and that the artisan could easily determine whether or not the gene encoding the variant polypeptide was amplified in colon tumors.

These arguments have been considered, but are also not deemed persuasive. First, in discussing the Wands factors, the breadth of the claims is excessive with regard to Applicants claiming all polypeptides at least 80% identical to SEQ ID NO:326 whose encoding polynucleotides are amplified in colon tumors. Applicants have only identified one specific polynucleotide sequence which is amplified in colon tumors (that encoded by ATCC No. 203129). Applicants have provided no guidance or working examples of any other polynucleotides encoding SEQ ID NO:326 which is amplified in colon tumors, or any polynucleotide which encodes a protein as much as 20% varied from SEQ ID NO:326. Furthermore, it would not be predictable to the artisan the function of any polypeptide which can be as little as 80% identical to SEQ ID NO:326, or that its encoding polynucleotides would be amplified in colon tumors. Respectfully, the test for enablement is "make and use" not "make and test."

Applicants also argue that the specification discloses methods for determining percent identity and that, once the polypeptide was identified, the specification teaches how to make such a protein and that "the claims currently recite polypeptide sequences associated with a biological activity of the

encoding polynucleotides. This biological activity together with the well-defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation."

Finally, these arguments have been considered, but are not deemed persuasive. Again, the test for enablement is "make and use" not "make and test." While the techniques for determining percent identity may be well-known in the art, Applicants have still not provided any guidance or working examples as to the function of the encoded protein which can vary as much as 20% from SEQ ID NO:326, regardless of the biological activity of its encoding polynucleotides. While the claims may now be limited to "native sequences" Applicants have not provided the function of these polypeptides, only a function of the encoding polynucleotides. Regardless, the specification does not provide sufficient guidance or working examples of either, as discussed in the previous paragraphs.

In summary, the breadth of the claims is excessive with regard to Applicants claiming all native sequence at least 80% identical to SEQ ID NO:326 without providing any guidance or working examples of these polypeptides other than the full-length SEQ ID NO:326 itself. Furthermore, it would not be predictable to the artisan which polynucleotides of these unknown polypeptides would be amplified in colon tumors. For these reasons, the Examiner maintains that undue experimentation would be required to practice the invention as claimed.

7. Claim Rejections - 35 USC § 112, first paragraph, written description

A. Claims 119-123 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 6-7 of the Office Action mailed 7/26/04. Applicants argue that the specification discloses methods for determining percent identity and that, once the polypeptide was identified, the specification teaches how to make such a protein and that the specific parameters (e.g. "native sequences") disclosed in the specification associated with "percent identity" would be considered "specific guidance."

These arguments have been considered, but are not deemed persuasive. While the techniques for determining percent identity may be well-known in the art, Applicants have still not provided adequate written description as to the function of the encoded protein which can vary as much as 20% from SEQ ID NO:326, regardless of the biological activity of its encoding polynucleotides. While

the claims may now be limited to "native sequences" Applicants have not provided the function of these polypeptides, only a function of the encoding polynucleotides. Regardless, the specification provides a written description of only one of these nucleic acid constructs amplified in colon tumors (SEQ ID NO:325). No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical nucleic acid residues which would structurally characterize the genus of nucleic acids encoding the genus of proteins claimed, because it is unknown and not described what structurally constitutes any different nucleic acids encoding these proteins, or nucleic acids encoding these proteins from any different species, which are further not described, or any different nucleic acid sequence encoding a polypeptide which "at least 80% identical" to SEQ ID NO:326; thereby not meeting the written description requirement under 35 USC 112, first paragraph.

8. Claim Rejections - 35 USC § 102

A. Claims 119-126 and 129-131 remain rejected under 35 USC 102 as being anticipated by Baker. Applicants argue that, based on their establishment of utility under 35 USC 101 they deserve priority prior to that of the Baker reference. However, as discussed in the above rejection under 35 USC 101, the priority date remains 11/14/01, the filing date of the instant invention.

9. Conclusion

A. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on T-F 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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